the column with water to remove inorganics and homocysteine, the desired product was obtained by further elution with 1 N ammonium hydroxide. Fractions containing the product were pooled and freeze-dried to give a fluffy, cream-colored solid: yield 845 mg (65%); mp indefinite; UV λ_{max} ($\epsilon \times 10^{-3}$) 262 nm at pH 1 (11.0), 262 nm at pH 7 (10.7), 265 nm at pH 13 (10.9); $[\alpha]^{23}_D$ +32.8 ± 0.7° (c 0.44, 1 N HCl); ^{1}H NMR (D_2O, chemical shifts in parts per million from DSS) 8.31 (s, H_8), 7.82 (d, H_2), 7.06 (d, $J_{2,3}$ = 6 Hz, H_3), 5.98 (d, $J_{2,3}$ = 6 Hz, $H_{1'}$), 4.65 (d of d, $J_{1',2'} = J_{2',3'}$ = 5 Hz, $H_{2'}$), 3.03 (m, $H_{5'}$), 2.78 (t, $J_{6',7'}$ = 8 Hz, $H_{6'}$), 2.23 (m, $H_{7'}$), $H_{3'}$, $H_{4'}$, and $H_{8'}$ were between δ 3.6 and 4.8 and were overlapping the solvent absorption; ^{13}C NMR [D_2O, chemical shifts referenced to internal dioxane and converted to the Me_4Si scale using the relationship δ_C (dioxane) = 67.4 ppm] 142.06, 140.36, and 139.20 (C_2, C_4, and C_8), 99.97 (C_3), 127.46 (C_5), 151.96 (C_6), 89.79 ($C_{1'}$), 74.20 ($C_{2'}$), 72.97 ($C_{3'}$), 84.30 ($C_{4'}$), 28.8 ($C_{5'}$), 34.5 and 31.5 ($C_{6'}$ and $C_{7'}$), 54.7 ($C_{8'}$), 175.29 ($C_{9'}$). Anal. ($C_{15}H_{21}N_5O_5S \cdot H_2O$) C, H, N.

S-(3-Deazaadenosyl)-DL-homocysteine (Racemic 9b). A cold (0–5 °C) solution of 3-deazaadenosine (**1b**; 265 mg, 1.0 mmol) in trimethyl phosphate (2.5 mL) was treated with thionyl chloride (290 μL, 4.0 mmol) and allowed to warm up to ambient temperature and held there for 20 h. The precipitate that formed was collected by filtration, washed thoroughly with ether, and quickly dried in vacuo: yield 330 mg (100%) of **5**; ^{1}H NMR (Me_2SO-d_6) δ 4.0 (m, 2 $H_{5'}$), 4.2 (m, $H_{3'}$ and $H_{4'}$), 4.5 (dd, $J_{1',2'} = J_{2',3'}$ = 5.2 Hz, $H_{2'}$), 6.05 (d, $J_{1',2'}$ = 5.2 Hz, $H_{1'}$), 7.34 (d, $J_{2,3}$ = 7 Hz, H_3), 7.83 (d, $J_{2,3}$ = 7 Hz, H_2), 8.7 (s, H_8); MS, *m/e* 330 (M^+), 295 [$(M - Cl)^+$], 284 [$(M - CH_2Cl)^+$], 134 [$(B + 1)^+$]. This material was added to a cold (ice–ethanol) solution prepared 30 min prior by adding DL-homocysteine thiolactone hydrochloride (203 mg, 1.32 mmol) with stirring to 1 N NaOH (4.6 mL). The resulting solution was refluxed for 3 h, neutralized with dilute HCl, and applied to a column of 100 mL of Dowex 50W-X4, 50–100 mesh, NH_4^+ form. After initial water elution to remove inorganics and unreacted starting material, the column was eluted with 1 N ammonium hydroxide to give the product. Fractions containing product were pooled and freeze-dried to give a glass: yield 245 mg (92%); MS, *m/e* 384 [$(M + 1)^+$]; UV λ_{max} ($\epsilon \times 10^{-3}$) 262 nm at pH 1 and 7 (9.97) and 265 nm at pH 13 (9.75); $[\alpha]^{24}_D$ +19.5 ± 0.5° (c 0.67, 1 N HCl); ^{13}C NMR (D_2O, see above) 141.95, 139.32, and 139.02 (C_2, C_4, and C_8), 99.75 (C_3), 127.13 (C_5), 151.45 (C_6), 89.80 ($C_{1'}$), 74.39 ($C_{2'}$), 72.96 ($C_{3'}$), 84.20 and 84.12 ($C_{4'}$), 28.73 ($C_{5'}$), 34.50 and 31.48 ($C_{6'}$ and $C_{7'}$), 54.70 ($C_{8'}$), 175.08 ($C_{9'}$).

5'-Deoxy-5'-iodo-3-deazaadenosine (7). A mixture of 3-deazaadenosine (**1b**; 2.00 g, 7.50 mmol), triphenylphosphine (2.84 g, 10.8 mmol), iodine (2.74 g, 10.8 mmol), and imidazole (1.54 g, 2.30 mmol) in dry toluene (400 mL) was stirred vigorously at 70 °C for 3 h and then the toluene was decanted. A methanol solution of the residue was applied to a dry column of silica gel (2 × 55 cm, Woelm). After the column was developed with chloroform–methanol (3:1), the product band was extracted with methanol, which was then evaporated to give the product as a glass: yield 1.29 g (46%); MS, *m/e* 134 [$(B + H)^+$], 248 [$(376 - HI)^+$], 376 (M^+).

The analytical sample was obtained in a small run which was purified by preparative thin-layer chromatography on silica gel plates developed with chloroform–methanol (3:1). Extraction of the product band with methanol gave a crystalline solid that was recrystallized from ethanol: mp 90–92 °C; UV λ_{max} ($\epsilon \times 10^{-3}$) 262 nm at pH 1 (10.6), 263 nm at pH 7 (10.5), and 264 nm at pH 13 (10.5); IR 2200–3000 cm^{-1} (br, hydrogen bonded NH^+). Anal. ($C_{11}H_{13}IN_4O_3 \cdot H_2SO_4$) C, H, N.

The picrate was obtained as a crystalline solid from an aqueous solution of picric acid and **7**. It was recrystallized from ethanol, mp 219–221 °C dec. Anal. ($C_{11}H_{13}IN_4O_3 \cdot C_6H_3N_3O_7$) C, H, N.

Analgesic Narcotic Antagonists. 9. 6-Methylene-8β-alkyl-*N*-(cycloalkylmethyl)-3-hydroxy- or -methoxymorphinans

Joseph O. Polazzi, Michael P. Kotick,*

Chemistry Department, Corporate Research Division, Miles Laboratories, Inc., Elkhart, Indiana 46515

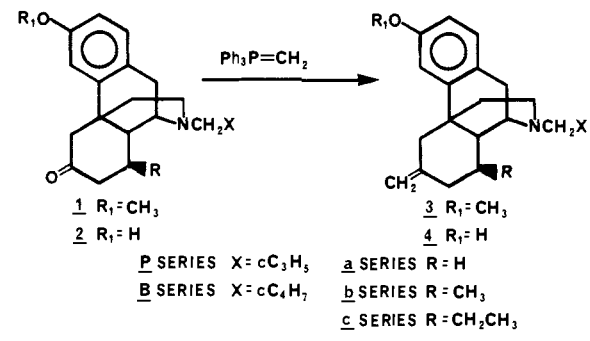
John F. Howes, and Ann R. Bousquet

Pharmacology Department, SISA, Inc., Cambridge, Massachusetts 02138. *Received May 1, 1981*

Series of *N*-(cyclopropylmethyl) (**P** series) or *N*-(cyclobutylmethyl) (**B** series) 3-methoxy (**1**) or 3-hydroxy (**2**) morphinan-6-ones with hydrogen (**a**), methyl (**b**), or ethyl (**c**) groups in the 8β position were converted to the 6-methylene compounds **3** or **4** by reaction with $Ph_3P{=}CH_2$. One member of this new series, *N*-(cyclobutylmethyl)-8β-methyl-6-methylenemorphinan-3-ol (**4Bb**), had potent mixed agonist–narcotic antagonist properties and, in contrast to the previously studied 6-oxo compound **2Bb**, did not substitute for morphine in dependent rats or monkeys.

We have recently been engaged in a program to prepare novel analgesic narcotic antagonists derived by chemical modification from the naturally occurring morphine alkaloids.[1] As an entry into this area, we initially explored the effect of lipophilic substitution at the 8β position in the C ring of dihydrocodeinone.[2] An extension of this work was the preparation of a series of *N*-(cycloalkylmethyl)-8β-alkylmorphinan-6-ones which had interesting pharmacological properties.[3] In order to extend these studies, we have now prepared and investigated the pharmacology of the 6-methylene derivatives of this latter series.

Scheme I



The replacement of the 6-oxo function in morphinone derivatives with other groups which are sp^2 hybridized has been reported. A summary of these studies[4] indicated that

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0022-2623/81/1824-1516$01.25/0

Table I. Agonist and Narcotic Antagonist Activity

6-methylene			6-oxo[a]		
	ED_{50}, μmol/kg sc (95% CL)[b]			ED_{50}, μmol/kg sc (95% CL)[b]	
compd	agonist: mouse writhing	antagonist: rat tail flick	compd	agonist: mouse writhing	antagonist: rat tail flick
3Pb	9.5 (5.4-16.5)	11.3 (5.3-24)	**1Pb**[c]	0.71 (0.4-1.3)	4.3 (1.4-12.7)
3Ba[d]	3.2 (1.6-6.0)	>20	**1Ba**[e]	0.58 (0.2-1.6)	IA 25[f]
3Bb[e]	16.5 (5.7-47)	14.1 (7.5-26)	**1Bb**[e]	1.38 (0.9-2.1)	16.4 (5.6-47)
4Pa	1.2 (0.8-1.8)	0.37 (0.07-1.8)	**2Pa**[g]	3.3 (1.3-8.4)	7.4 (4.1-13)
4Pb	5.3 (2.3-12)	0.89	**2Pb**	10.2	1.8
4Pc	IA 30	2.8 (0.8-9.8)	**2Pc**[e]	IA 50	4.7 (3.1-6.8)
4Ba[e]	0.22 (0.14-34)	>24	**2Ba**[e]	0.047 (0.006-0.34)	IA 25
4Bb	0.53 (0.15-1.8)	2.5 (0.98-6.1)	**2Bb**[e]	0.29 (0.03-2.9)	2.8 (0.98-8.0)
4Bc	>28	21.2 (13.5-33)	**2Bc**[e,g]	0.54 (0.33-0.77)	0.82 (0.49-1.4)
			butorphanol	0.34 (0.13-0.90)	2.0 (0.96-9.4)
			cyclazocine	0.41 (0.11-1.66)	0.81 (0.48-1.44)
			pentazocine	12.9 (8.7-19.3)	36.4 (13.6-100)
			nalorphine	3.5 (0.58-21.4)	2.5 (0.46-13.5)
			naloxone	IA	0.11 (0.03-0.3)
			naltrexone	>28	0.2 (0.1-0.3)

[a] Data from ref 3. [b] Reference 16. [c] See ref 17 for studies with this compound. [d] Tartrate salt. [e] HCl salt. [f] IA, inactive at dose indicated. [g] Short duration; ED_{50} at 5 min.

such changes at C6 do not adversely affect the potency or the agonist–antagonist character of the parent drug. Most relevant to our work was the report that replacement of the oxygen at C6 by a methylene group in naloxone or naltrexone results in enhanced antagonist activity and oral potency.[6] No reports were found in the literature which describe similar modification at C6 in *N*-(cycloalkylmethyl)morphinan compounds lacking the 4,5α-epoxy bond.

Chemistry. The 6-methylene derivatives **3** and **4** (Scheme I) were prepared by reaction of the corresponding 6-oxo compounds **1** and **2** with an excess of methylenetriphenylphosphorane in Me_2SO.[6,7] The NMR signal for the 6-methylene protons in **3** and **4** was observed as a broad singlet at ca. δ 4.55–4.68 in $CDCl_3$ solution. The low yield realized in the preparation of methoxy compounds **3** was due to difficulties in obtaining a clean separation of the excess, nonalkaloid material from the desired product by column chromatography. Attempted purification of **4Pb** by selective extraction, prior to chromatography, resulted in only a low recovery of the desired product.

Results and Discussion

Compounds were tested for agonist activity in the acetic acid induced mouse writhing[8] assay. Narcotic antagonist activity was determined against an ED_{80} of morphine in the modified rat tail-flick procedure.[9] The results are recorded in Table I, as are the data previously reported[3] for the corresponding compounds **1** and **2** in the 6-oxo series. Conversion of **1** to **3** decreases agonist potency and moderates antagonist activity. For the phenolic compounds **4**, the same trends in agonist–antagonist activity are observed as noted with the 6-oxo compounds **2**. The previously reported[3] tendency of the 8β-methyl group to enhance antagonist activity, while not substantially affecting agonist potency, is clearly evident in the *N*-(cyclobutylmethyl) series.

The secondary pharmacology of **2Bb** has been reported.[3,10] Continuous infusion of **2Bb** followed by cessation of treatment caused mild withdrawal symptoms in rats. Single-dose studies with this drug following chronic morphine administration in the rat indicated partial suppression of the withdrawal syndrome.[10] In contrast, no indications for abstinence were noted following long-term administration of **4Bb** to rats. Substitution of **4Bb** for morphine in dependent rats caused marked precipitation of withdrawal. Pharmacological studies with **4Bb** in the rat will be published elsewhere.[11]

Drug substitution studies with **2Bb** in morphine-dependent monkeys, showed that this 6-oxo compound was able to partially substitute for morphine.[12] In contrast, similar tests with methylene derivative **4Bb** demonstrated that this compound did not substitute for morphine at doses of 1, 2, or 4 mg/kg in single-dose suppression studies.[13] This drug also caused the appearance of withdrawal symptoms in the dose range of 0.125 to 8.0 mg/kg. The onset of action was rapid and the duration of activity was longer than that observed with naloxone (administered at 0.05 mg/kg).

Studies have shown that **4Bb** is active in agonist and antagonist assays when administered to animals by the oral route. The potency and onset of action of this agent indicate very rapid and thorough absorption by this method of administration.

This work has shown that the conversion of 6-oxomorphinans to the corresponding 6-methylene derivatives does not substantially increase, or alter, the agonist–antagonist potencies of these molecules. Remarkably, the small structural change of compound **2Bb** to the corresponding 6-methylene compound **4Bb** resulted in an an-

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Table II. Methylenemorphinans 3 and 4

compd	X	R	R_1	% yield free base[a]	mp, °C	recrystn solvent[b]	formula[c]
3Pb	c-C_3H_5	CH_3	CH_3	80	91-93	E	$C_{23}H_{31}NO$
3Ba	c-C_4H_7	H	CH_3	26	89-91[d]	E	$C_{23}H_{31}NO \cdot C_4H_6O_6 \cdot 0.5EtOH$
3Bb	c-C_4H_7	CH_3	CH_3	37	221-224[e]	EE-T	$C_{24}H_{33}NO \cdot HCl$
4Pa	c-C_3H_5	H	H	58	220-223	E	$C_{21}H_{27}NO$
4Pb	c-C_3H_5	CH_3	H	21[f]	231-233	E	$C_{22}H_{29}NO$
4Pc	c-C_3H_5	CH_2CH_3	H	62	197-200	E	$C_{23}H_{31}NO$
4Ba	c-C_4H_7	H	H	87	155[g]	A	$C_{22}H_{29}NO \cdot HCl \cdot C_3H_6O$[h]
4Bb	c-C_4H_7	CH_3	H	82	165-169	EE-H	$C_{23}H_{31}NO$
4Bc	c-C_4H_7	CH_2CH_3	H	84	166-168	C	$C_{24}H_{33}NO$

[a] Yield of purified free base after chromatography. [b] A = acetone; C = chloroform; E = ethanol; EE = ethyl ether; H = hexane; T = toluene. [c] All compounds had C, H, and N analysis within ±0.4% of the calculated value. [d] *d*-Tartrate salt, hemiethanol solvate. [e] Hydrochloride salt. [f] Selective extraction prior to workup. [g] Foams, hydrochloride salt, acetone solvate. [h] Acetone.

algesic drug which does not substitute for morphine in rats or monkeys. *N*-(Cyclobutylmethyl)-8β-methyl-6-methylenemorphinan-3-ol (**4Bb**) is currently undergoing further evaluation.[14,15]

Experimental Section[16]

Preparation of *N*-(Cycloalkylmethyl)-3-methoxy- or -hydroxy-6-methylenemorphinans (3 or 4). A solution of $Ph_3P{=}CH_2$[7] was prepared from NaH (14.4 mmol) and Ph_3PCH_3Br (5.14 g, 14.4 mmol) in Me_2SO (30 mL) under an argon atmosphere. To this was added a solution of **1** (6 mmol) or **2** (4 mmol) in Me_2SO (20 mL), and the reaction mixture was stirred at 80 °C in a preheated oil bath for 1 h. The cooled solution was diluted with ice–water–NH_4OH and extracted with 3 portions of toluene. The combined organic extracts were washed 4 times with H_2O, dried, and evaporated to a crude residue, which was chromatographed. Pure fractions were combined on the basis of TLC and evaporated to dryness, and the residue was crystallized directly or converted to the salt as indicated in Table II.

Acknowledgment. The authors thank Drs. R. N. Schut, J. E. Villarreal, and R. K. Razdan for their continued interest and encouragement.

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(16) Methods have been reported. See ref 1 or 2. The presence and the amount of solvent in **3Ba** and **4Ba** were confirmed by NMR in an appropriate solvent. For pharmacological testing, compounds which were prepared as salts were administered in distilled H_2O; free bases were dissolved by the dropwise addition of 1 N HCl and then further diluted. For both agonist and antagonist assays, at least five animals per dose and at least three doses of each drug were utilized in determination of the ED_{50} or AD_{50} values.
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Substituted Imidazo[1,2-*a*]pyridine-2-carbamate Anthelmintics

Richard J. Bochis,* Leonard E. Olen, Frank S. Waksmunski, Helmut Mrozik, Philip Eskola, Peter Kulsa,

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

George Wilks, Joyce E. Taylor, John R. Egerton, Dan A. Ostlind, and George Olson

Merck Institute for Therapeutic Research, Rahway, New Jersey 07065. *Received January 14, 1981*

Anthelmintic efficacies of a series of 6-substituted methyl imidazo[1,2-*a*]pyridine-2-carbamates were compared to similarly substituted benzimidazole-2-carbamates. With only one exception, methyl 6-benzoylimidazo[1,2-*a*]-pyridine-2-carbamate, both classes of compounds exhibited similar activity vs. *Nematospiroides dubius* in mice. Preliminary screening indicated methyl 6-(1,2,2-trichloroethenyl)imidazo[1,2-*a*]pyridine-2-carbamate to be the most potent derivative in the series. However, evaluation in sheep indicated that its anthelmintic spectrum was inferior to methyl 6-(phenylsulfinyl)imidazo[1,2-*a*]pyridine-2-carbamate.

A similarity of structure–activity relationships with benzimidazole anthelmintics has been described for imidazo[1,2-*a*]pyridines.[1] This research has been extended to phenyl thioether derivatives, resulting in the discovery of methyl 6-(phenylsulfinyl)imidazo[1,2-*a*]pyridine-2-carbamate (**1a**) as a potent, broad-spectrum anthelmintic.[2] This report compares anthelmintic structure–activity relationships between benzimidazoles and imidazo[1,2-*a*]-pyridines.

Structures **2a–e** include most of the commercially useful benzimidazole-2-carbamate anthelmintic agents.[3-7] The

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